

Effect of Consumption of Extravirgin Olive Oil on the Lipid Profile and on the Glycemia of Children with Cystic Fibrosis Seen at a Specialized Center in Belém-PA/ Brazil

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Abstract— Introduction: Cystic fibrosis (CF) is a genetic disease that affects the cystic fibrosis transmembrane conductance regulatory protein (CFTR), which functions as a chlorine channel regulating the balance between ions and water across the epithelium. Nutrition has shown an important role in this problem due to the need for a differentiated dietary prescription through a hypercaloric and hyperlipidic diet associated with anthropometric monitoring, and as a food strategy extra virgin olive oil can bring several benefits due to its rich composition in acids. monounsaturated fatty acids (MUFA) and their bioactive compounds considered nutraceuticals, capable of modulating gene expression, interfering with the production of proteins and metabolites; It has anti-inflammatory, antioxidant and antimicrobial effects. Method: A clinical trial was carried out with children aged 2 to 11 years attended at the João de Barros Barreto University Hospital, at this age there were 20 children, 2 could not be contacted and 3 refused to participate, so the research had 15 individuals, the exposure group (n=8) received dietary monitoring and extra virgin olive oil for three months and the control group (n=7) the standard nutritional guidance for the disease. The variables were: lipid profile (total cholesterol, HDL, LDL and triglycerides), glycemic status (fasting glucose). Results: There was a reduction in the rates of fasting glucose ($p=0.0355$) and triglycerides ($p=0.0157$) with a significant difference when comparing the control and intervention groups. Discussion: no other study was found using the ingestion of pure extra virgin olive oil in people with cystic fibrosis, only studies with a mixture

of olive oil and soy or docosahexaenoic acid, however, regarding the healthy population and other diseases, the tests that were significant fasting glucose and triglycerides were found several studies that demonstrate the benefit of olive oil in reducing these rates. Conclusion: Supplementation with extra virgin olive oil proved to be effective, however several factors can influence the health of these people such as lifestyle habits, general health status and individual genetic variants, so studies with longer intake time and with a greater number of participants, preferably multicenter, should be evaluated, but extra virgin olive oil is shown as another tool to aggregate the various measures to improve the quality of life of this population.

I. INTRODUCTION

Cystic fibrosis is a genetic and multisystemic disease that affects several excretory organs such as: lung, pancreas, intestine, sweat glands, many factors can contribute to the survival of these individuals, such as access to transplantation, specialized centers, use of pancreatic enzyme replacement (PERT), therapeutic innovations, adequate treatment of infections and neonatal screening^{1,2}.

In addition to these aspects, nutrition and the maintenance and improvement of growth have been shown to be a key factor for the survival of these patients. A cohort study comparing the survival of Boston patients who consumed a low-fat diet resulted in short stature and malnutrition, whereas Toronto patients who consumed a high-fat diet had improved nutritional status and survival, with average life expectancy 30 years of life in Toronto and 21 years in Boston, demonstrating a great importance in the consumption of fat and an adequate nutritional intervention³.

The nutritional recommendation indicated for CF is a hypercaloric and hyperlipidic diet, fractionated and with high energy density, with 120% to 150% of the recommended food consumption (RDA) and in severe cases or infections 200% of the RDA and regarding the distribution of macronutrients 40% of the total caloric value of lipids, 40% to 50% carbohydrates and 15% to 20% proteins⁴.

Even with nutritional monitoring and despite the benefits of high fat intake, the lipid profile of this population is often altered, in general LDL and total cholesterol are below the tolerable limit, however with pancreatic degradation LDL can be increased and triglycerides, and HDL levels are lower than recommended⁵, this change can be caused by chronic inflammation, use of corticosteroids, pancreatic insufficiency, liver diseases and a high-carbohydrate diet⁶.

After respiratory disease and exocrine pancreatic disease, abnormalities in glycemic status and diabetes are the main complications in CF, CFTR mutation leads to increased

glucose levels, insulin resistance to diabetes through a gradual loss of mass. of beta cells with disease progression⁷. These changes, such as dyslipidemia, chronic inflammation and changes in blood glucose, are common in cystic fibrosis, however adequate nutritional management is a fundamental strategy of great relevance in improving the quality of life of this population.

Combined with specific nutritional monitoring in this disease, this study proposes the use of extra virgin olive oil due to the possibility of bringing several benefits to patients with cystic fibrosis, as they have nutritional properties that can positively influence its main diseases.

Extra virgin olive oil was recognized for its benefits from the dissemination of the Mediterranean diet as a protective factor and reduced risk of mortality and incidence of diseases such as cancer, cardiovascular and neurodegenerative diseases^{8,9}. These effects are attributed to its high oleic acid content, monounsaturated fatty acid that can come from different sources, with beef as the main animal source, and vegetable present in olive oil, canola oil, avocado and oilseeds.

However, the isolated action of oleic acid seems to be beneficial depending on which food it comes from, as a meta-analysis study showed that only the oleic acid present in olive oil is effective in reducing the risk for all causes of mortality studied, such as stroke and cardiovascular mortality¹⁰.

Oleic acid has a favorable molecular mechanism for cholesterolemia, as it does not increase total cholesterol and LDL-cholesterol compared to saturated fat¹¹ by decreasing the free cholesterol pool in the cell, as it is a substrate for the cholesterol acyltransferase (ACAT) enzyme that induces cholesterol esterification¹². Due to its action in lipogenic and lipolytic pathways, this acid is able to prevent excess deposition of triacylglycerol in the liver, having a favorable effect on liver tissue in addition to an anti-inflammatory effect¹³.

Currently, these positive effects of extra virgin olive oil have also been attributed to its phenolic portion, which has among its main classes: hydroxytyrosol, oleuropein, simple phenols, lignans, flavonoids and secoiridoids¹⁴. These substances are able to modulate gene expression, interfering with protein expression and the production of metabolites, the phenolic fraction of extra virgin olive oil has several benefits such as: anti-inflammatory, antioxidant and antimicrobial effects¹⁵.

Its anti-inflammatory power has been compared to that of ibuprofen¹⁶, including in terms of CF, some studies recommend the use of ibuprofen sporadically, as it seems to delay the decline in lung function and lead to nutritional improvement, especially in children¹⁷, so the use of olive oil could be an important complementation combined with the need to use anti-inflammatory drugs without the side effects of these drugs. For all the factors listed, these compounds have been shown to be relevant in the protection of chronic degenerative diseases, diseases related to aging, among others.

Therefore, the consumption of extra virgin olive oil can be of great value to patients with cystic fibrosis, as the antimicrobial effect of the oil may help to fight the pulmonary infection that is very recurrent in this disease, in addition to acting on the increased need for fat due to the high energy expenditure due to lung disease, it may also benefit them in terms of improving glucose control, lipid profile and reduction of inflammatory markers.

II. METHOD

A clinical trial was carried out from August 2021 to March 2022 in patients with cystic fibrosis treated at the cystic fibrosis outpatient clinic of Hospital Universitário João de Barros Barreto (HUIBB), children aged 2 to 11 years of both were included in the study. sexes residing in Belém or in nearby cities, so that they could follow up properly.

In the age group studied, there were 26 children 6 lived in other states or in distant municipalities and were not available to participate, which was one of the exclusion criteria of the research, so only 20 were able to participate in the research, a call was made in the message groups, and posters allocated in the clinic to capture these patients, it was possible to contact 18 patients in total, however 3 refused to participate, so the study had a sample of 15 children, the groups were divided by age group (CG- control group: 7 and GI- intervention group: 8).

Subjects were randomly recruited according to the visit to the clinic for routine consultations, which occur monthly or every 3 months depending on the child's health condition, and received standard nutritional counseling for the disease,

guided by the hospital nutritionist, to the intervention group were given monthly bottles of extra virgin olive oil and recommended supplementation of 10% of the daily energy value of lipids, according to each age group during the 3-month period, all participants underwent examinations at baseline (T0) and at the end (T1) of the survey.

In the current literature, there is no standardized dose of extra virgin olive oil consumption, so a measurement was made according to the recommended lipids for this population in a way that provides nutritional benefits, but without any health problems, given that this population has difficulty digesting fats. Therefore, the recommended dose was calculated according to the total energy value of the Institute of Medicine (2000) for healthy individuals, plus 50% for patients with CF (150%), in which 40% of the energy value was considered to be from lipids and so, according to this value, 10% extra virgin olive oil was added, in addition to the oil, they received a meter with the exact marking for correct consumption.

The extra virgin olive oil used was of the same brand from the beginning to the end of the study, (Gallo®) traditional in the Brazilian market and of easy access, the bottle delivered to the participants was de-characterized so that it could not lead to doubts about conflict of interests, it was used if the same batch -345S0861, the HPLC test - High Performance Liquid Chromatography was carried out, to evaluate: acidity, peroxide value, moisture, acidity index, melting point, specific density, saponification index, unsaponifiable matter, oxidative stability and fatty acid profile.

The trademark in question is in accordance with Normative Instruction No. 1, of January 30, 2012 (amended by Normative Instruction No. 24, of June 18, 2018) of the Ministry of Agriculture, Livestock and Supply (MAPA), which establishes the Technical Regulation of olive oil and olive pomace oil and the tolerance limits, in addition to being included in the list of olive oils inspected by MAPA that comply with the legal standard.

The project followed all ethical principles in accordance with the guidelines contained in CNS resolution, 466/2012, MS and was submitted to the HUIBB Ethics Committee, approved on March 15, 2021-Opinion Number: 4,591,897. The participants were duly informed about the research and the Free and Clarified Consent Term was signed by the guardian or the Free and Clarified Term of Assent, in the case of children over 6 years old.

Biochemical tests were evaluated from the glycemic profile by means of fasting glucose test, the lipid profile by means of total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL).

As for the genetic profile, the results of the genetic test that present the variant (cDNA) and the alleles of the genotype were verified, already performed in the routine with outpatients.

Regarding the statistical analysis, categorical variables were presented as numbers (percentages) and continuous variables with normal distribution were expressed as mean \pm , standard deviation and analyzed using Student's t test for paired samples, while those with non-normal distribution were presented as median; IIQ and analyzed by the

Wilcoxon test. Numerical variables were evaluated for normality and homogeneity of variances using the Kolmogorov-Smirnov test and Levene test, respectively. Statistical analyzes were performed using the Prism 6.1 program, and the significance level adopted was 5%.

III. RESULTS

As for the demographic profile, the participants had an approximate number of females and males, most were 11 years old (46.6%) were from the inner city of Pará.

Table 1- Demographic data

		Freq	
		n=15	%
Gender	Male	8	53.3
	Female	7	46.7
Age	2	1	6.7
	3	1	6.7
	4	1	6.7
	5	2	13.3
	6	1	6.7
	8	2	13.3
	11	7	46.6
Origin	Belém	4	26.7
	Inner city of Pará	11	73.3

Source: Authors, 2022

Regarding the lipid profile of the patients, most of them had adequate cholesterol (80%), and adequate LDL (93.3%), however, HDL was shown to be below adequate, with only one patient with normal rates in terms of triglycerides. also showed relevant data being more than 30% borderline or elevated.

Table 2- Lipid profile

		Freq	
		n=15	%
Cholesterol	Desirable	12	80.0
	Borderline or elevated	3	20.0

	Boderline	2	13.3
	Elevated	1	6.7
HDL			
	Suitable	1	6.7
	Inadequate	14	93.3
LDL			
	Suitable	14	93.3
	Inadequate	1	6.7
Triglycerides			
	Desirable	10	66.7
	Boderline	1	6.7
	Elevated	4	26.7

Source: Authors, 2022

There were no patients with altered fasting glucose.

Table 3- Fasting blood glucose

	Freq n=15	%
Glycemia		
Suitable	15	100.0

Source: Authors, 2022

The variant (cDNA) most frequently was F508del, only three participants had other genetic mutations.

Table 4- Genetic variants identified

		Freq n=15	%
c.1521_1523delCTT	F508del	12	80.0
c.1624G>T	G542X	2	13,3
c.3846G>A	W1282X	1	6.7

Source: Author, 2022

There was a preponderance of heterozygosity, that is, different mutations in each of the alleles studied.

Table 5- Alleles

	Freq n=15	%
HET	9	60.0

HOM

6

40.0

Source: Authors, 2022

Table 6- Statistical analysis

	Control (Average±DP/Median; IIQ)	Intervention (Average; DP/Median; IIQ)	p Value
Cholesterol	119.1±40.7	114.3±33.2	0.4700 ^a
HDL	38.6±9.2	38.1±12.2	0.7751 ^a
LDL	62.0; 26.0	54.0; 28.0	0.8506 ^b
Triglycerides	71.0; 61.0	57.0; 15.5	0.0157 ^b
Glycemia	89.2±8.3	86.7±6.1	0.0355 ^a

Source: Authors, 2022

^a Paired t-Student Test^b Wilcoxon Test

IV. DISCUSSION

Based on the results, there was a significant result regarding the reduction of triglyceride levels and fasting blood glucose, from the ingestion of olive oil, demonstrating important results in several aspects, given the various morbidities associated with CF.

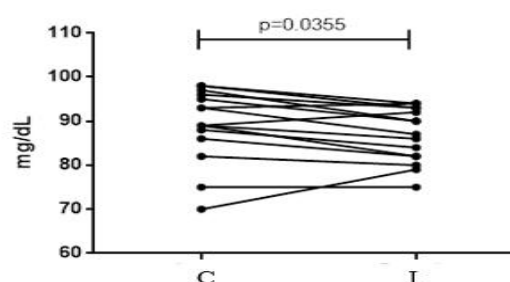
It is important to note that to date, no other studies were found using the ingestion of pure extra virgin olive oil in people with cystic fibrosis, only studies with a mixture of olive oil and soy or docosahexaenoic acid.

GLYCEMIA

People with CF can eventually develop diabetes due to insulin deficiency, as cystic fibrosis affects the endocrine cells of the pancreas over time, particularly the beta cells that produce insulin, higher blood glucose levels promote bacterial colonization in the lungs, as a result, negatively affect lung function and increase the risk of mortality¹⁸.

Findings demonstrate that glycemic abnormalities can start very early in cystic fibrosis, possibly due to insufficient insulin secretion¹⁹. However, the patients who participated in the study did not present changes in blood glucose at the time of the research, this may have occurred because, even with possible glycemic abnormalities in childhood, the prevalence of diabetes in this population increases with age,

so that it affects most of the patients who participated in the study patients over 40 years old²⁰, which differs from the profile studied, but the statistical results show that with the consumption of extra virgin olive oil there was a reduction in blood glucose levels.



Graph 1- blood glucose after 3 months of ingestion of olive oil.

Source: Authors, 2022

The polyphenols in extra virgin olive oil can affect glucose metabolism by inhibiting the digestion and absorption of carbohydrates, reducing glucose release from the liver and/or stimulating glucose uptake in peripheral tissues. Its antioxidant properties may decrease the development of

glycosylated products, such as HbA1cAs, and lead to reductions in glycemic load. The consecutive attenuation in insulin secretion, as well as the increase in sensitivity, may explain the beneficial effects on glycemic control²¹.

The postprandial phase plays an important role in glycemic control, as it is associated with the abrupt formation of reactive oxidant species and the glycemic profile²². In a 2018 study²³, it was shown that oleuropein, a component of extra virgin olive oil, had a positive effect on postprandial blood glucose and oxidative stress due to its antioxidant property, through tests such as serum glucose and insulin concentration, among others.

In a survey that sought to evaluate extra virgin olive oil in the prevention and management of type 2 diabetes mellitus from a systematic review and meta-analysis of cohort studies and intervention trials, four cohort surveys and 29 randomized controlled trials were analyzed, some relevant data were found:

-Meta-analysis on risk of DM2

It was found that the combined association of olive oil use was inversely associated with a lower risk of T2DM. The dose-response meta-analysis revealed that each daily increase of 10 g of olive oil was associated with a 9% reduction in the risk of T2DM, a non-linear relationship between olive oil intake and the risk of T2DM was also observed. The risk of T2DM decreased by 13% with increasing olive oil intake up to ~15-20 g day.

-Meta-analysis on glycemic control

Olive oil interventions resulted in a significantly more pronounced reduction in HbA1c compared to the respective control groups. Stratified analyzes for age, study design, study duration, olive oil administration, and olive oil type confirmed the results of the main analysis. A stronger reduction in HbA1c was observed in studies with T2DM patients <60 years with extra virgin olive oil supplementation²⁴.

In a systematic review and meta-analysis we evaluated the effects of diets high in MUFA monounsaturated fatty acids (12% MUFA of total energy content) versus low MUFA diets (< 12% MUFA of total energy content) by through tests of fasting glucose, fasting insulin, glycosyl hemoglobin and evaluation of the homeostasis model in individuals with type 2 DM2 diabetes, glucose intolerance and hyperinsulinemia. It was concluded that a diet rich in MUFA causes significant short- and long-term reductions in plasma glucose in individuals with DM2 and, therefore, should be recommended as a nutritional strategy²⁵.

In a recent survey with the Brazilian diet, positive results were also found²⁶, a study was carried out that evaluated the effects of extra virgin olive oil alone and in combination with a traditional Brazilian diet on inflammatory markers

and glycemic profiles in adults with DM2 and class II obesity/ III. The intervention with Olive Oil + Brazilian Diet effectively decreased the levels of fasting insulin, IL-1 α and adiponectin, suggesting its beneficial role in improving inflammatory profiles and fasting insulin levels in adults with class II/III obesity and T2DM.

The quality of fat consumed in the diet of people with CF may be important in terms of blood glucose, according to the findings of this research, in addition to the other studies cited that report the benefits of consumption of extra virgin olive oil in people without CF, but regarding glycemic changes It is also important to be careful when choosing carbohydrates, as foods with a low glycemic load can be beneficial for glycemic control also in HR^{27,28}, and combined with extra virgin olive oil, it could further potentiate its effects on glucose control.

LIPID PROFILE

Lipotoxicity in CF is described as an imbalance within the phospholipids of the cell membrane between Saturated Fatty Acids (SFA) and Unsaturated Fatty Acids (UFA). The CFTR mutation results in several dysfunctions that may be responsible for changes in the action of fatty acids available to the cells, with an excess of saturated fatty acids at the expense of unsaturated fatty acids, mainly in bronchial epithelial cells. Pancreatic insufficiency and cystic fibrosis-related liver disease lead to bad absorption of polyunsaturated fatty acids (PUFA), and hypoxia preventing the desaturation steps necessary to form UFA from SFA²⁹.

It is important to emphasize that people with CF and pancreatic insufficiency are at risk of developing dyslipidemia³⁰, so this data suggests that the traditional focus on a diet rich in carbohydrates and fats for CF needs to be readjusted, because with the improvement in the quality of treatment of people with CF these are living longer, so it is necessary that nutritional recommendations focus more on the quality of ingested fat than on the quantity³¹, so extra virgin olive oil can be a good nutritional strategy for this population.

In a study that sought to investigate the effect of the ingestion of extra virgin olive oil enriched with phenolic compounds alone or in combination with thyme on the blood lipid profile of people with hypercholesterolemia, and to understand if the generated modifications were related to changes in the populations and activities of the intestinal microbiota, resulted in the ingestion of an extra virgin olive oil enriched with phenolic compounds and thyme for 3 weeks decreased blood LDL in hypercholesterolemic humans. This cardioprotective effect may have been mediated by the increase in populations of bifidobacteria together with the increase in microbial metabolites of phenolic compounds with antioxidant activities, such as

protocatechuic acid and hydroxytyrosol. Specific stimulation of the growth of bifidobacteria in the human intestine suggested a potential prebiotic activity of extra virgin olive oil enriched with phenolic compounds and thyme³².

In addition to the benefit of lowering LDL in hypercholesterolemic patients, the stimulation of bifidobacteria may be important for people with CF, as the interactions of the immune system and microbes, especially in early life, influence a lower risk of allergies, asthma and other inflammatory diseases. This action, which is initiated with breastfeeding, guides healthier relationships between the immune system and the microorganisms of the intestinal microbiota, providing them with nutrients that, in turn, benefit the host's immune system through probiotics such as bifidobacteria³³.

As people with CF need a strengthened immune system due to recurrent infections characteristic of the disease, mainly pulmonary, the possible prebiotic, immunoprotective action that can modulate plasma lipids of extra virgin olive oil seems positive for these individuals.

In a study³⁴ that investigated the composition of plasma phospholipids and triglycerides of fatty acids in patients with CF submitted to a dietary supplement consisting of a mixture of 50% extra virgin olive oil and 50% soybean oil, fourteen young people, aged between 6 and 15 years, affected by cystic fibrosis, with pancreatic insufficiency and heterozygotes or homozygotes for the delta F508 mutation. Patients on the supplemented diet achieved significant increases in the relative amount of oleic acid in triglycerides, as well as a significant decrease in saturated fatty acids, in addition, the ratio between linoleic acid and arachidonic acid significantly increased in triglycerides, in phospholipids the relative amount of linoleic acid and palmitic acid increased significantly. These results showed that oleic acid can be absorbed and incorporated into the plasma triglycerides of patients with CF who receive pancreatic enzymes.

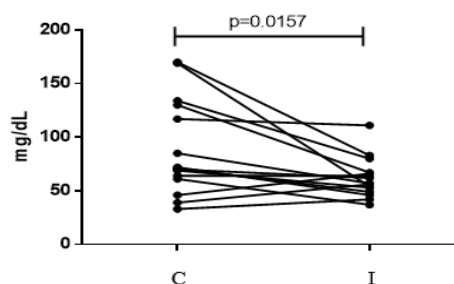
A randomized crossover study was carried out at 6 research centers in 5 European countries with 200 healthy adult male volunteers. Participants were randomly assigned to 3 sequences of daily administration of 25 mL of 3 oils. The oils had low (2.7 mg/kg of olive oil), medium (164 mg/kg) or high (366 mg/kg) phenolic content, but they were similar, the intervention periods were 3 weeks. The results showed an increase in high-density lipoprotein (HDL) levels for olive oil with low, medium and high polyphenol content, the total cholesterol-HDL cholesterol ratio decreased linearly according to the phenolic content of the oil, triglyceride levels decreased for all oils, oxidative stress markers decreased with increasing phenolic content, mean changes

for oxidized low density lipoprotein levels for low, medium and high polyphenol oil.

Despite the short ingestion period, the study concluded that extra virgin olive oil is more than a monounsaturated fat, and its phenolic content may also have benefits for plasma lipid levels and oxidative damage³⁵.

A network meta-analysis survey of 30 human intervention studies aimed to analyze the exact role of olive oil in modifying metabolic factors (glucose and circulating lipids), as despite its beneficial role, it is not entirely clear whether its effects on health are due to the presence of monounsaturated lipids and/or the antioxidant fraction of the microconstituents present in olive oil. The work found that lower levels of antioxidant polyphenols may be sufficient for the beneficial effects of olive oil, and the lipid fraction of olive oil may be responsible for some of its beneficial actions. LDL is mediated by adherence to the Mediterranean diet, olive oil polyphenols play an important role in increasing HDL-cholesterol and improving the antioxidant and inflammatory status of individuals, in all parameters examined, the beneficial effect of olive oil was more evident in individuals with established metabolic syndrome or other chronic conditions/diseases³⁶.

It is important to emphasize that in the study above, regarding the satisfactory result of the union of the consumption of olive oil with the Mediterranean diet, it could be adapted from foods frequently consumed in the Amazon region, as there is a study with a proposal to adapt the Mediterranean diet using foods from the Amazon region considering the similarity criteria: energy content; macronutrient composition (carbohydrates, proteins and/or fats); and/or presence of micronutrients or substance with the same functional claim using regional foods³⁷, demonstrating that they could be easily incorporated into the diet of CF patients who participated in the research.



Graph 2 – Triglycerides after 3 months of ingestion of olive oil.

Source: Authors, 2022

V. CONCLUSION

The study showed that the regular consumption of extra virgin olive oil can be beneficial for children with cystic fibrosis, the findings that show a reduction in fasting glucose levels, triglycerides corroborate this hypothesis, however several factors can influence the health of people with CF such as: life habits (diet, physical activity, daily hours of sleep, among others), general health status (mental health, immunity, infections, exacerbations, etc.), and also genetic variants with great influence individual, all these factors have a strong influence on the health of these people, extra virgin olive oil is shown as another tool to add the various measures to improve the quality of life of this population.

It is important to emphasize that the regular consumption of the oil in addition to the dose are important factors for the action of the bioactive compounds and must be individually evaluated by the team that accompanies the patient so that it can be properly used and added to their routine in the most pleasant way feed.

Intervention time and the fact that CF is a rare disease, which makes it difficult to capture a more robust sample, were adversities found in the study, therefore, further research with a longer time and with a greater number of participants and preferably multicenter should be evaluated so that they can add up and arrive at more solid scientific evidence.

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